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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Robert Michael ROBERTS
Jonathan Andrew GREEN and
Sancai XIE

Serial No.: 09/273,164

Filed: March 19, 1999

For: COMPOSITIONS AND METHODS FOR EARLY PREGNANCY DIAGNOSIS

Group Art Unit: 1643

Examiner: L. Cook

Atty, Dkt. No.: UVMO:003

CERTIFICATE OF MAILING
37 C.F.R. §1.8

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January 13, 2003
Date

Robert E. Hanson

SUPPLEMENTAL BRIEF ON APPEAL

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BRIEF ON APPEAL

BOX AF
Commissioner of Patents
Washington, D.C. 20231

Sir:

This brief is filed (in triplicate) in response to the Final Office Action mailed on January 2, 2002, and the Notification of Non-Compliance With 37 C.F.R. §1.192(c) mailed November 12, 2002. This Brief replaces the Appeal Brief mailed in the case on August 15, 2002. The date for filing the instant Brief is January 13, 2003, based on the mailing date of the Notification of Non-Compliance With 37 C.F.R. §1.192(c) and the Petition for Extension of Time of one-month below. The fees for the brief were paid with the Appeal Brief mailed August 15, 2002 and the fees for extension of time are enclosed herewith. Please date stamp and return the attached postcard as evidence of receipt.

PETITION FOR EXTENSION OF TIME

Pursuant to 37 C.F.R. §1.136(a), Appellants petition for an extension of time of one month, to and including January 13, 2003, in which to file this Supplemental Appeal Brief. The fee for the extension is enclosed. Should any other fees be due under 37 C.F.R. §1.17, the Commissioner is authorized to deduct such fee from or Fulbright & Jaworski Deposit Account No. 50-1212/10012519/10056.

I. REAL PARTIES IN INTEREST

The real parties in interest are the assignee of the case, The Curators of the University of Missouri, and the licensee thereof, Monsanto Company.

II. RELATED APPEALS AND INTERFERENCES

There are no interferences or appeals for related cases.

III. STATUS OF THE CLAIMS

Claims 1-8, 10-14, 30-34 and 182-183 were pending at the time of the final Office Action. Claims 1, 3-9 and 30-34 were finally rejected. Claims 9, 15-29, and 35-181 were cancelled during prosecution and thus claim 1, 3-8 and 30-34 are currently pending and the subject of this appeal. A copy of the appealed claims is attached as Appendix 1.

IV. STATUS OF AMENDMENTS

Subsequent to the final Office Action, an Amendment pursuant to 37 C.F. R. §1.113 was mailed by Applicants on April 2, 2002, and an Amendment under 37 C.F.R. §1.116 was filed with the Appeal Brief on August 15, 2002. Neither amendment was entered by the Examiner.

V. SUMMARY OF THE INVENTION

The invention relates to a method for detecting pregnancy in a bovine animal comprising using an antibody that binds immunologically to at least one pregnancy associated antigen (PAG) that is present in early pregnancy and absent at about two months post-partum. Specification from page 4, line 20 to page 5, line 6. The invention is significant because it allows pregnancy detection early and in animals that have been rebred after calving, which customarily is done within 2 to 3 months post-partum. Specification from page 3, line 26 to page 4, line 16.

VI. ISSUES ON APPEAL

A. Are claims 1, 3, 5, 6 and 14 anticipated under 35 U.S.C. §102(b) by Roberts *et al.* (1995)?

B. Are claims 1, 3, 5, 6 and 13 anticipated under 35 U.S.C. §102(b) by Zoli *et al.* (1992)?

C. Are claims 4, 7 and 8 obvious under 35 U.S.C. §103(a) over Roberts *et al.* (1995) or Zoli *et al.* (1992) in view of Sasser *et al.* (1989)?

D. Are claims 30-34 obvious under 35 U.S.C. §103(a) over Roberts *et al.* (1995) and Zoli *et al.* (1992) in view of Xie *et al.* (1997) and Gerrie *et al.* (1986)?

VII. GROUPING OF THE CLAIMS

The claims stand or fall together for purposes of the appeal.

VIII. SUMMARY OF THE ARGUMENT

The references cited by the Examiner do not teach all elements of the claims and no teachings have been alleged by the Examiner which could support such a conclusion. Claim 1, upon which each of the appealed claims directly or indirectly depends, describes a method for detecting pregnancy in a bovine animal that comprises use of an antibody that binds immunologically to at least one pregnancy associated antigen that is *present in early pregnancy and absent at about two months post-partum*. None of the references cited by the Examiner, either alone or in combination, teach pregnancy associated antigens or antibodies thereto that are both present early and absent about two months post-partum, as required by the claims. Without such a teaching, the claims can neither be anticipated nor rendered obvious.

VIII. ARGUMENT

A. The Claims are Not Anticipated by Roberts et al. (1995)

Claims 1, 3, 5, 6 and 14 were finally rejected under 35 U.S.C. §102(b) as anticipated by Roberts *et al.* (1995) (Exhibit A). The examiner characterizes the reference as teaching evaluation of maternal serum concentrations for PAGs, and correlating measurement to pregnancy in cattle and sheep. However, Roberts *et al.* (1995) does not teach PAGs meeting the claim limitations. Claim 1, upon which each of the remaining claims depends, reads as follows:

> 1. A method for detecting pregnancy in a bovine animal comprising:
>
> (a) obtaining a sample from said animal; and
>
> (b) contacting said sample with an antibody that binds immunologically to at least one pregnancy associated antigen (PAG), wherein said PAG is present in early pregnancy and absent at about two months post-partum; and

(c) detecting said PAG bound to said antibody;

whereby the presence of said PAG in said sample indicates that said animal is pregnant.

Roberts *et al.*, however, does not disclose a PAG that is "present in early pregnancy and absent at about two months post-partum." For example, in the last two sentences of the first full paragraph on page 233 of Roberts *et al.*, it is indicated that the disclosed PAG, "PAG-1", had an apparent long half-life and that "[b]ecause concentrations at term may be well above 1 μg/ml, *it requires at least 3 months for levels to drop back to threshold values* (Fig. 1), and cows are customarily bred within 2 to 3 months after calving." Emphasis added. A review of the referenced Fig. 1, which is also given in Zoli *et al.* (1992), demonstrates this same phenomenon, showing that mean bPAG levels were above 1 ng/ml at 80 days post-partum. A review of the Zoli *et al.* abstract, indicates that the undetectable level for serum bPAG levels was less than 0.20 ng/ml. It is thus evident that Roberts *et al.* does not teach PAGs meeting the claim limitations.

Based on an earlier telephonic interview in the case, it is believed by Applicants that the position of the Examiner relies, at least in part, on the belief that the PAG taught by Roberts *et al.* could potentially be viewed as within the scope of the claims because of the use of the term "*about* two months post-partum." Emphasis added. However, the PAG described by Roberts *et al.* is indicated to be present at least ***three*** months post-partum. This cannot be said to be "about two months", as this is a figure 50% greater than two months. The term "about" is well known to those of skill in the art and does not allow for such a discrepancy. For example, the Encarta™ online dictionary (http://dictionary.msn.com), gives the meaning of the relevant usage of the word as a preposition as "approximately: close to in number, time, or degree." Exhibit F. The relevant definition of "about" from the online version of the Merriam Webster's Collegiate

Dictionary™ (http://www.m-w.com) is "reasonably close to." Exhibit G. Therefore, an interpretation of "about two months" to include three months simply does not fit the meaning of the term as it is understood by those of skill in the art. Without teaching such a PAG, the cited reference cannot anticipate the claims.

Appellants finally note that the Examiner has provided no basis for concluding that Roberts *et al.* teaches the PAGs required by the instant claims other than to make the conclusory allegation that the "prior art teaches such PAGs." For example, the one-paragraph rejection contained in both the first and the final Office Action states that the PAG in Roberts *et al.* was "expressed just prior to implantation until term (~145 days in sheep, ~280 days in cattle)." However, this is irrelevant to the claimed subject matter, which specifies immunologic detection of at least one PAG that is "present in early pregnancy and absent at about two months post-partum." What is relevant, and is not even alleged by the Examiner, is that the PAG be *absent about two months post-partum*. The above-cited portions of Roberts *et al.* clearly indicate it is not. The rejection by the examiner thus fails on its face to present any basis that could be used to reject the claims.

It is the burden of the Examiner, in a rejection under 35 U.S.C. § 102(b), to show that each and every element as set forth in the claim is found in the prior art. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). To the extent that unexpressed inherent characteristics form the basis of an anticipation rejection, it must be shown that these characteristics necessarily flow from the disclosure. *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) ("To

serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.") The Examiner has clearly failed to meet this burden. Accordingly, the rejection must fail.

In view of the foregoing, reversal of the rejection is respectfully requested.

B. The Claims are Not Anticipated by Zoli et al. (1992)

Claims 1, 3, 5, 6 and 13 were finally rejected under 35 U.S.C. §102(b) as anticipated by Zoli *et al.* (1992) (Exhibit B). The reference was cited as disclosing a double-antibody RIA for BoPAGs, and measuring BoPAG levels during pregnancy in cows.

Appellants again note that the cited reference fails to teach PAGs meeting the claim limitations. For example, attention is drawn to the Abstract of Zoli, which indicates that peripheral serum bPAG concentrations were 1.44 +/- 1.08 ng/ml at day 90 post partum. Thus the mean bPAG concentration of at least 0.36 ng/ml at 90 days post-partum was nearly twice the indicated undetectable level of <0.20 ng/ml that was given in Zoli *et al.* At most, the level was 2.52 ng/ml, or more than 10 times the undetectable level. As admitted in both the first and the final Office Action, the undetectable concentration was not reached until day 100 +/- 20 pp.

The problem created by the late presence of the Zoli *et al.* PAG is acknowledged on page 89 of Zoli *et al.*, where it is stated that "[o]verall, the presence of bPAG in sera for nearly 100 days pp constitutes a problem for subsequent diagnosis of pregnancy by this method if rebreeding occurs less than 80 days pp." Thus, again, the mean bPAG levels detected by Zoli *et al.* did not drop below undetectable levels until ***more than 3 months post-partum***. Even if one were to assume that the Zoli *et al.* bPAG was present at least 80 days post-partum, this figure

cannot be considered to be "about two months" As described above, the term "about" has a well known meaning in the art of close or reasonably close to a referenced figure. However, 80 days is approximately 33% longer than two months. This is cannot reasonably be construed to be "close" in time to two months. As such, the absence of this element from the prior art means that an anticipation rejection will not stand.

Reversal of the rejection is thus respectfully requested.

C. Claims 4, 7 and 8 are Not Obvious Under 35 U.S.C. §103 over Roberts et al. (1995) or Zoli et al. (1992) in view of Sasser et al. (1989)

Claims 4, 7 and 8 were finally rejected as obvious over Roberts *et al.* (1995) or Zoli *et al.* (1992) in view of Sasser *et al.* (1989) (Exhibit C). In particular, Roberts *et al.* and Zoli *et al.* were cited as above and Sasser *et al.* was cited as teaching use of saliva, milk or urine as samples to PAG.

As indicated above, regardless of what Sasser *et al.* may or may not disclose regarding means of sampling PAGs, it clearly does not address the material element of "at least one pregnancy associated antigen (PAG), wherein said PAG is present in early pregnancy and absent at about two months post-partum." The Examiner has not alleged otherwise. Further, Sasser *et al.* indicates that the PAG studied, "PSPB," was previously found to "remain[] in the serum for a considerable time after parturition in cows" and that "[t]his long half-life poses a problem for pregnancy testing in re-mated post-partum cows." Sasser *et al.* at page 111, third full paragraph. Therefore, the Examiner has not shown that the prior art teaches or suggests all of the limitations of the claims, as is required under 35 U.S.C. § 103. *See, e.g., In re Vaeck* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Absent such a teaching, one of skill in the art would lack a

reasonable expectation of success in arriving at the claimed invention. Therefore, the claims cannot be considered obvious.

In view of the foregoing, Appellants respectfully request reversal of the rejection.

D. Claims 30-34 are Not Obvious Under 35 U.S.C. §103 over Roberts et al. (1995) and Zoli et al. (1992) in view of Xie et al. (1997) and Gerrie et al. (1986)

Claims 30-34 remain rejected over Roberts *et al.* (1995) and Zoli *et al.* (1992) in view of Xie *et al.* (1997) (Exhibit D) and Gerrie *et al.* (1986) (Exhibit E). Roberts *et al.*, Zoli *et al.* and Xie *et al.* are cited as above and Gerrie *et al.* is cited as teaching an ELISA for PAG.

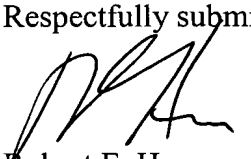
In response, Appellants first point out that the human pregnancy-associated α2-glycoprotein is completely unrelated to the PAGs being discussed here. Thus, to the extent that the examiner is attempting to extrapolate more from Gerrie *et al.* than an ELISA based-assay for diagnosing pregnancy, Appellants submit that such is not merited. In fact, it should be pointed out that a variety of different assay formats may be employed according to the present invention, including but not limited to ELISA, RIA, Western blot, dot-blot and lateral flow technology.

More to the point, and irrespective of what Gerrie may or may not disclose regarding human PAGs, it clearly does not address the material element of "at least one pregnancy associated antigen (PAG), wherein said PAG is present in early pregnancy and absent at about two months post-partum." That is, Gerrie *et al.*, just like Roberts *et al.*, Zoli *et al.* and Xie *et al.*, provides no indication that such PAGs even exist. For example, Xie *et al.* is directed to sheep (ovine) PAGs that are related to the bovine PAG-1 discussed in Roberts *et al.* Abstract, Xie *et al.* It, therefore, remains pure hindsight to argue that any of these references can suggest, with sufficient motivation or the requisite likelihood of success, the currently claimed invention. Thus, in light of the foregoing, Appellants respectfully request reversal of the rejection.

IX. CONCLUSION

It is respectfully submitted, in light of the above, none of the pending claims are anticipated under 35 U.S.C. §102(b) or obvious under 35 U.S.C. §103(a). Therefore, Appellants request that the Board reverse the pending grounds for rejection.

Respectfully submitted,



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Date: January 13, 2003

APPENDIX 1: APPEALED CLAIMS

1. A method for detecting pregnancy in a bovine animal comprising:.

   (a) obtaining a sample from said animal; and

   (b) contacting said sample with an antibody that binds immunologically to at least one pregnancy associated antigen (PAG), wherein said PAG is present in early pregnancy and absent at about two months post-partum; and

   (c) detecting said PAG bound to said antibody;

   whereby the presence of said PAG in said sample indicates that said animal is pregnant.

2. The method of claim 1, wherein said PAG is selected from the group consisting of PAG2, PAG4, PAG5, PAG6, PAG7 and PAG9.

3. The method of claim 1, wherein said sample is saliva, serum, blood, milk or urine.

4. The method of claim 3, wherein said sample is saliva.

5. The method of claim 3, wherein said sample is serum.

6. The method of claim 3, wherein said sample is blood.

7. The method of claim 3, wherein said sample is milk.

8. The method of claim 3, wherein said sample is urine.

10. The method of claim 1, wherein said detection comprises detection of bovine PAG (BoPAG) 2, BoPAG4, BoPAG5, BoPAG6, BoPAG7, BoPAG9, BoPAG 7v; BoPAG9v; BoPAG 15; BoPAG 16; BoPAG 17; BoPAG 18; BoPAG 19; BoPAG 20 or BoPAG 21 with polyclonal antisera.

11. The method of claim 1, wherein said detection comprises detection of bovine PAG (BoPAG) 2, BoPAG4, BoPAG5, BoPAG6, BoPAG7, BoPAG9, BoPAG 7v; BoPAG9v; BoPAG 15; BoPAG 16; BoPAG 17; BoPAG 18; BoPAG 19; BoPAG 20 or BoPAG 21 with a monoclonal antibody preparation.

12. The method of claim 9, wherein said detection comprises ELISA.

13. The method of claim 9, wherein said detection comprises RIA.

14. The method of claim 9, wherein said detection comprises Western blot.

30. The method of claim 1, further comprising detecting a second PAG in said sample.

31. The method of claim 30, further comprising detecting a third PAG in said sample.

32. The method of claim 12, wherein said ELISA is a sandwich ELISA comprising binding of a PAG to a first antibody preparation fixed to a substrate and a second antibody preparation labeled with an enzyme.

33. The method of claim 32, wherein said enzyme is alkaline phosphatase or horseradish peroxidase.

34. The method of claim 32, wherein said first antibody preparation is monoclonal.